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10/706,852	11/12/2003	Gary L. Griffiths	329575	6078

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/706,852	GRIFFITHS ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-21,23-55,57-89 and 91-125* is/are pending in the application.

4a) Of the above claim(s) *43-55, 57-89, 91-118, 120-124* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-21,23-41 and 125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 11/30/2004
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made of applicants election of Group I. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 1-21, 23-41, 43-55, 57-89, 91-118, 120-124 have been amended. Claims 22, 56 and 90 have been canceled. Claims 1-21, 23-55, 57-89 and 91-125 are pending. Claims 43-55, 57-89, 91-118, 120-124 are withdrawn as being drawn to non-elected inventions. Claims 1-21, 23-41 and 125 are examined on the merits..

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: The prior applications 10/314,330, 10/350,096, 10/377,122 fail to provide a written description of the instant claims composition comprising nanoparticles or any submicron particles conjugated to a CD74 binding molecule and in combination with one or more effectors. Accordingly, the instant application will be given the effective priority date commensurate with the disclosure of 60/478,830, June 17, 2003, which describes CD74 binding molecules conjugated to nanoparticles.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9-21, 23-35, 38, 39 and 125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A)As drawn to a anti-CD74 "binding molecule" and binding molecules which specifically bind to the antigens recited in claim 11.

The instant claims are drawn to a genus of CD-74 binding molecules. claim 11 further specifies the incorporation of other antigen "binding molecules". When given the broadest reasonable interpretation, the term binding molecule directed to CD74 or the antigens recited in claim 11 read on any molecule which so binds, including small non-peptide molecules. The instant specification provides a written description of only antibodies which bind to CD74. the art recognizes antibodies which bind to the antigens recited in claim 11. The description of an antibody fails to describe the claimed genus of compounds because said genus tolerated members which differ significantly in structure from that of an antibody which binds to the target antigen.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated,

does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406.

In the instant case the binding molecules are distinguished only by function. One of skill in the art would reasonable conclude that applicant was not in possession of the genus of cd74 binding molecules or the binding molecules of the antigens recited in claim 11.

(B)As drawn to a generic "binding molecule" and a generic "oligonucleotide"

Claim 21 requires that the composition comprise an effector which is a "binding molecule" or an "oligonucleotide". Neither the specification nor the claims provide a target or a structure fro the binding molecule; neither the specification not the claims provides a function for the "oligonucleotide". Thus the genus for each of the binding molecule and the oligonucleotide is not limited by structure or function and the specification does not define any members of either genus. define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. Thus, the binding molecules and oligonucleotide of claim 21 fail to meet the written description requirements.

(C)As drawn to a fusion protein comprising all or part of the heavy and light chains of the antibody fragment that bind to CD74

Claims 38 and 39 are drawn in part to a fusion protein which comprises part of all of the heavy and light chains of the anti-CD74 antibody fragment. The contemplation of such a fusion protein does not provide an adequate description of the fusion protein. The art recognizes that formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order

to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Thus the contemplation of a fusion protein which will bind to CD74 and comprises part of the heavy and light chains of antibodies which bind to CD74 does not provide any structural characteristic for said fusion protein because "part" of the heavy and light chains can be a single amino acid. The specification has failed to describe a single fusion protein which has the claimed characteristic. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use the claimed fusion proteins.

Claims 11, 12, 21, 30, 31, 32, 33, 34, 39 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for effectors which are drugs, toxins, radioisotopes or a photodyanimc agent, and CD74 binding antibodies, does not reasonably provide enablement for antibodies which bind to CD74 which are multispecific and inclusion of further binding molecules which bind to antigens which are not known to be related to the B cell dyscrasias or hematopoietic cells expressing MHC II, such as CD4, CD5, CD8, CD40L (also known as gp39 and CD154) MUC1, MUC2, MUC3, MUC4, tenascin, VEGF, EGFR, CEA, placental growth factor, carbonic anhydrase IX, CSAp and IlGF, and effectors which are immunomodulators, enzymes, hormones, or antiangiogenic molecules listed in claim 34, CD74 binding multispecific molecules which target antigens which are not CD74 or diabodies, triabodies and tetrabodies which bind to CD74. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn in part to a composition comprising one or more anti-CD74 binding molecules conjugated to one of more lipids, polymeric carriers, micelles or nanoparticles and one or more effectors, further comprising binding molecules which specifically bind to T cells via CD4, CD5, CD8, the MUC antigens, tenascin, carbonic anhydrase IX, vascular endothelial growth factor receptor, epidermal growth factor receptor, carcinoembryonic antigen,

CSAp, which is a colon-specific antigen peptide, and IlGf, which is insulin-like growth factor. The instant specification states that CD74 expressing diseases are "immune dysfunction diseases, autoimmune disease, graft vs host, organ graft disease, a solid tumor, non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, , B cell malignancy, or a T cell malignancy and that solid tumors include melanomas, carcinomas, sarcomas and/or gliomas. The specification has not provided any objective evidence that non-hematopoietic solid tumors express CD74. The prior art teaches that the LL1 antibody is a CD74 binding antibody (Hansen et al, Biochemical Journal, 1996, Vol. 320, pp. 293-300, see page 296, first column, lines 18-19) and that the LL1 antibody is specific for B lymphocytes , monocytes, and histiocytes (Juweid et al, Nuclear Medicine Communications, 1997, vol. 18, pp. 142-148, see lines 1-2 of the abstract) because it binds to the Ii (invariant chain) of the MHC II antigen, and lacks cross reaction with solid tumors, multiple myelomas and myelogenous leukemia (Juweid et al, ibid, page 147, second column, last sentence). The specification describes the treatment of Burkitt's lymphoma cell lines, Jurkat lymphoblastic T-cell leukemia and HL-60 myelmonocytic leukemia cells with the anti-CD74 lipid emulsions of the invention (page 77, paragraph 123-124) but fails to provide objective evidence that the anti-CD74 antibody bound to any of the non-B cells. Neither the specification nor the prior art provides evidence that the CD74 antigen is expressed on solid tumor types such as carcinomas or sarcomas. Neither the specification nor the prior art teach that T cell malignancies, multiple myelomas or myelogenous leukemias can react with an antiCD74 antibody. The specification fails to teach an alternate reason for including a biding agent which targets a non CD74 expressing cell in a composition with an anti-CD74 binding agent. Because the art teaches against the cross reaction of an anti-CD74 antibody with solid tumors, myelomas and myelogenous leukemias and because the instant specification provides no objective evidence for this binding, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use the broadly claimed instant composition which includes binding agents which target cells not expressing the CD74 antigen.

Claim 21 requires in part effector molecules which are enzymes, or hormones. Claim 30 requires and effector molecule which is an enzyme. Claim 34 requires that the composition of claim 1 further comprise anti-angiogenic molecules. For the reasons set forth above, the

specification is nonenabling for the targeting of cancer cells which are not those known in the prior art to express the invariant chain of the MHC II receptor. The specification has not taught how to use an enzyme or a hormone in a composition which comprises a CD74 binding molecule which is targeted to the known cancer cell types which express the MHC II invariant receptor, such as B cell malignancies and Hodgkin's lymphoma. The specification has not taught how to use a composition comprising an antiangiogenic molecule out of the context of a solid tumor and therefore one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use the broadly claimed invention as it encompasses effectors which are enzymes and hormones.

Claim 39 requires that the fusion protein of claim 39 is multivalent and multispecific. when given the broadest reasonable interpretation, the term "multispecific" includes binding molecules which target antigens other than CD74. Claim 41 requires a diabody, triabody or tetrabody. Hannsen et al teach (Biochemical Journal, 1996, Vol 320, pp. 293-300) that the invariant chain of MHC II is rapidly internalized and that antibodies binding thereto are catabolized (page 298, second column, lines 1-7). Hannsen et al teach that this rapid uptake can be used to deliver toxins, radioisotopes, drugs that can kill tumor cells expressing Ii, such as B-cell lymphoma (page 299, second column, lines 1-5 of the last paragraph). The specification fails to teach a use for a CD74 binding molecule which is multispecific. One of skill in the art would reasonable conclude that if a multispecific binding protein which includes CD74 binding were administered to a patient having b cell lymphoma, the non-CD74 specificity would interfere with the internalization of the antibody and prevent a specific therapeutic effect directed at the B lymphoma tumor cells. Claim 41 requires a diabody, triabody or tetrabody. These binding molecules include multispecific binding molecules and binding molecules which target only CD74. The multispecific diabodies triabodies and tetrabodies are not enabled for the same reasons as those set forth above. The species that bind solely to CD74 are also not enabled because they would cause crosslinking between different invariant chains and nether the art nor the specification provides a mechanisms for internalization of such a cross linked species. Given the lack of guidance in the specification regarding his issue or teachings regarding an alternative use for the multispecific binding protein of claim 39, or the diabodies, triabodies and tetrabodies

of claim 41, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use the broadly claims composition.

Claim 21 requires and effector which is an immunomodulator. Claim 32 is drawn to the composition of claim 1 comprising an immunomodulator. Claim 33 requires an immunomodulator which comprises various interleukins, interferons, G and GM colony stimulating factors. The art recognizes that interleukins such as Il6 and Il-10 contributed to the developments and pathogenicity of B cell lymphomas (abstract of Breen et al, Clinical Immunology, 2003, vol. 109, pp. 119-129 and the abstract of Nagel et al, Leukemia, 2005, vol. 19, pp. 841-846). The specification has not provided guidance on how to use the requires interleukins and cytokines to treat B cell lymphomas which could potentially stimulate and/or increase the malignant cells

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 6, 8, 20, 21, 24, 25, 26, 28, 29, 35 and 125 are rejected under 35 U.S.C. 102(b) as being anticipated by Juweid et al (Nuclear Medicine Communications, 1997, Vol. 18, pp. 142-148).

Juweid et al disclose a 99Tcm-LL1 antibody conjugate in a sulfur colloid as a carrier (abstract) which meets the limitations of claims 1 requiring a micelle, claim 2 requiring a emulsion, claim 6 wherein the anti-CD74 antibody is conjugated to one or more micelles, and claim 8 requiring a fragment of LL1. Juweid et al disclose that theLL1 Fab fragment was labeled with 99Tcm using 99Tcm-pertechnetate which meets the limitations of the chelator of claim 24 (page 143, first column, line 7-10)..

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10, 13-21, 27, 35, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pawlak-Byczkowska et al (Cancer Research, 1989, Vol. 49, pp. 4568-4577) as evidenced by Juweid et al (Nuclear Medicine Communications, 1997, Vol. 18, pp. 142-148) in view of Lundberg et al (Journal of Pharmacy and Pharmacology, 1999, Vol. 51, pp. 1099-1105) and Hansen et al (Biochemical Journal, 1996, Vol. 320, pp. 293-300)..

Pawlak-Byczkowska et a teach that the EPB-1 monoclonal antibody, which is identified by Juweid et al to be the LL1 antibody (Juweid, ibid, page 142, second column, last two lines). Pawlak-Byczkowska et a teach that the EPB-1 antibody discriminated between lymphoid and non-lymphoid tissue and did not cross react with solid tumor tissue specimens (abstract). Pawlak-Byczkowska et al suggest that the antibody is n appropriate candidate for radioimmunodetection and radioimmuntherapy of B cell neoplasms (page 4568, second column, lines 5-10). Pawlak-Byczkowska et al do not teach the specific composition comprising a LL1 conjugate and one or more effectors.

Lundberg et al teach conjugation of the LL2 antibody (which is the Pawlak-Byczkowska EPB-2 antibody, Lundberg, ibid, page 1099, first column, lines 8-10) with a long-circulating

drug carrier lipid emulsion. Lundberg et al tech that submicron lipid emulsions have hydrophobic cores which can solubilize considerable amounts of lipophilic drugs(page 1099, second column, lines 12-14), which fulfills the specific embodiment of claim 7 requiring a nanoparticle.. Lundberg et al teach that because LL2 is internalized into cells it facilitated intracellular delivery of cytotoxic agents (page 1099, column 1-2, bridging sentence). Lundberg et al teach that the problem or rapid uptake by mononuclear phagocytes is overcome by engrafting polyethylene chains on the particle surfaces with the monoclonal antibody linked to the distal PEG terminus(page 1100, first column, lines 1-9). Lundberg et al teach the conjugation of the antibody to a lipid by a sulfide linkage to PEG (Figure 1). Lundberg et al teach the lipids of DPPc and DPPe which fulfill the embodiment of claim 13 requiring amphiphilicity. Lundberg et al teach the reaction of DSPE with the distal terminus of the PEG chain thus fulfilling the specific limitation of claim 14 requiring a nucelophilic carbon (page 1100, first column, last seven lines). Lundberg et al teach a maleimide group at a distal terminus (Figure 1, top structure) thus fulfilling the embodiments of claim 15-19. The 99-Tcm of Lundberg fulfills the specific embodiment of a diagnostic agent and a radioisotope.

Hansen et al teaches that the LL1 antibody is rapidly internalized on cells expressing the MHC I invariant chain (page 295, second column) as measured by a 111-In chelate of DTPA (page 293, second column, lines 13-14). Hansen et al suggest that the LL1 antibody is useful for the delivery of toxins, drugs or radioisotopes that can kill tumor cells expressing surface Ia, such as B cell lymphomas (page 299, last paragraph).

It would have been prima facie obvious at the tie the claimed invention was made to substitute the LL1 antibody for the LL2 antibody in the composition taught by Lundberg et al. One of skill in the art would have been motivated to do so by the teaching of Hannsen regarding the ability of LL1 to be rapidly internalized and the suggestions by both Pawlak-Byczkowska et al and Hansen et al that the LL1 antibody is useful for targeting B cell lymphomas and other B cell malignancies that express the invariant chain antigen bound by LL1.

Claims 1-10, 13-21, 27, 35-38 and 125 rejected under 35 U.S.C. 103(a) as being unpatentable over Pawlak-Byczkowska et al, Juweid et al, Lundberg et al and Hansen et al as

applied to claims 1-10, 13-21, 27, 35, and 125 above, and further in view of Schlom (In: Molecular Foundations of Oncology, Sameule Broader, Ed, 1991, pages 95-134)..

Schlom teaches that in all of the previous reported human trials in which non-immunosuppressed patients were treated with multiple doses of murine antibodies only the first and perhaps the second dose of said antibody was efficiently reaching the tumor site due to the HAMA response. Schlom teaches that it is unrealistic to assume that just one or two administrations of any anti-cancer therapeutic would be effective. Schlom teaches that the answer to this problem is the humanization of the murine antibodies (pages 97-98, bridging paragraph). Schlom also teaches that F(ab')2 or Fab' fragments also help reduce the HAMA response (page 119 second column, lines 16-17 under the heading "Single Chain Antigen Binding Proteins). Schlom also teaches that scFv although comparable in binding affinity to FAb' have a more rapid plasma clearance than the Fab' fragment resulting in a greater tumor to tissue ratio. Schlom also points out that the small size of the scFv improves the capacity for penetration through the tumor mass.. Schlom also points out that scFv are easier to make than F9ab')2 of Fab' fragments.

It would have been prima facie obvious at the time the claimed invention was made to provide a humanized LL1 antibody or a humanized LL1 antibody fragment, such as an scFv. One of skill in the art would have been motivated to do so by the teachings of Schlom on the necessity of avoiding the HAMA response.

Claims 1-10, 13-21, 27, 35-38, 40 and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pawlak-Byczkowska et al, Juweid et al, Lundberg et al, Hansen et al and Schlom as applied to claims 1-10, 13-21, 27, 35-38 and 125 above, and further in view of Greenwood et al, 'Effector functions of attached sets of recombinant human IgG subclass antibodies', In: Protein engineering of antibody molecules, for therapeutic and Prophylactic Applications in Man, Clark, Ed., 1993, pages 89 and 97).

Greenwood et al teach that for some applications it may be necessary to use an antibody isotype which is non depleting and merely targets the antigen (lines 5-6), such as IgG4, or any of theIgG2 or IgG3 which have less ability to activate complement and ADCC.

It would have been prima facie obvious at the time the claimed invention was made to use a human constant region which was IgG2a or Ig3 or Ig4. One of skill in the art would have been motivated to do so in order to have a "non-depleting" antibody which functions to bind and be rapidly internalized with and effector molecule which is a radioisotope, toxin or drug. One of skill in the art would have been motivated to o so by the teachings of Hannsen et al on the rapid internalization of the LL1 antibody and the suggestion by Greenwood et al that some applications require only a antibody targeting function.

Claims 1-10, 13-21, 23, 27, 35, and 125 rejected under 35 U.S.C. 103(a) as being unpatentable over Pawlak-Byczkowska et al, Juweid et al, Lundberg et al and Hansen et al as applied to claims 1-10, 13-21, 27, 35, and 125 above and in further view of Nakagawa et al, (Journal of Neurooncology, 1999, vol. 45, pp. 175-183).

Claim 23 embodies the composition of claim 21 further comprising FUdR-dO Nakagawa et al teach the treatment of a patient with metastatic lymphoma to the brain with 5-fluoro-doxyuridine (Table 1, patient #16).

It would have bee prima facie obvious to one of skill in the art to use FUdR-dO within the liposomes taught by Lundberg to target non-cranial B lymphoma cells. One of skill in the art would have been motivated to do so by the suggestion by Lundberg et al that the liposomes are good carriers of drugs and the teachings of Hannsen et al on the internalization of antibodies which bind to the CD74 receptors which are present on lymphoma cells. One of skill in the art would have concluded that the killing of the cranial metastatic lymphoma cells by intrathecal administration was indicative that lymphoma cells targeted by the LL1 antibody would be similarly sensitive to the FUdR-dO.

Claims 1, 2, 6, 8, 11, 20, 21, 24-26, 28, 29, 35 and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Juweid et al (Nuclear Medicine Communications, 1997, Vol. 18, pp. 142-148 in view of Goto et al (Blood, 1994, vol. 84, pp. 1922-1930).

Juweid et al teach a 99Tcm-LL1 antibody conjugate in a sulfur colloid as a carrier (abstract) which meets the limitations of claims 1 requiring a micelle, claim 2 requiring a emulsion, claim 6 wherein the anti-CD74 antibody is conjugated to one or more micelles, and

claim 8 requiring a fragment of LL1. Juweid et al teach that theLL1 Fab fragment was labeled with 99Tcm using 99Tcm-pertechnetate which meets the limitations of the chelator of claim 24 (page 143, first column, line 7-10). Juweid et al teach that the LL1 antibody does not react with multiple myeloma (page 147, last sentence)

Goto et al teach an additional B cell restricted antigen, HM1.24 which is a target for late-stage B cell maturation and multiple myeloma.

One of skill in the art would have been motivated to combine targeting of CD74 which does not bind to multiple myeloma with targeting of HM1.24 for multiple myeloma in order to have a reagent for screening which would detect both malignancies.

All claims are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.

4/17/2007

KAREN A. CANELLA, Ph.D
PRIMARY EXAMINER